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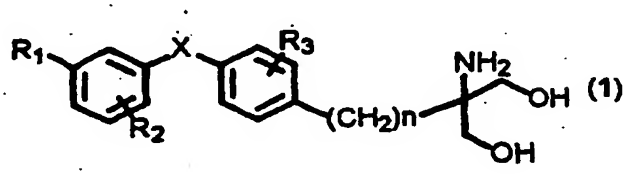
(54) DIARYL SULFIDE DERIVATIVE, ADDITION SALT THEREOF, AND IMMUNOSUPPRESSANT

(57) The present invention provides diaryl sulfide derivatives that exhibit significant immunosuppressive effects with less side effects.

The diaryl derivatives of the present invention are represented by the following general formula (1):



One example is 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propanediol.

EP 1 431 284 A1

Description

TECHNICAL FIELD

[0001] The present invention relates to diaryl sulfide derivatives, salts and hydrates thereof that are useful as an immunosuppressive agent.

TECHNICAL BACKGROUND

[0002] Immunosuppressive agents are widely used as a treatment for autoimmune diseases such as rheumatoid arthritis, nephritis, osteoarthritis and systemic lupus erythematosus, chronic inflammatory diseases such as inflammatory bowel disease, and allergic diseases such as asthma and dermatitis. Progress in medicine has led to an increase in the number of tissue and organ transplantations performed each year. In such a situation of modern medicine, having as much control as possible over the rejection following transplantation is a key to successful transplantation. Immunosuppressive agents also play a significant role to this end.

[0003] Among immunosuppressors commonly used in organ transplantation are antimetabolites, such as azathioprine and mycophenolate mofetil, calcineurin inhibitors, such as cyclosporin A and tacrolimus, and corticosteroid, such as prednisolone. Despite their popularity, some of these drugs are not effective enough while others require continuous monitoring of the blood drug level to avoid renal failure and other serious side effects. Thus, none of conventional immunosuppressive agents are satisfactory in view of efficacy and potential side effects.

[0004] Multiple drug combined-therapy, in which different immunosuppressive drugs with different mechanisms of action are used, is becoming increasingly common with the aims of alleviating the side effects of the drugs and achieving sufficient immunosuppressive effects. Also, development of new types of immunosuppressive agents that have completely different mechanisms of action is sought.

[0005] In an effort to respond to such demands, the present inventors conducted a search for new types of immunosuppressive agents with main emphasis on 2-amino-1,3-propanediol derivatives.

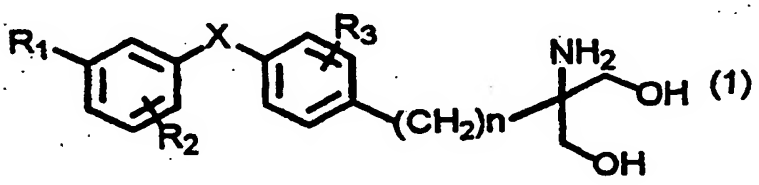
[0006] While the use of 2-amino-1,3-propanediol derivatives as immunosuppressive agents has been disclosed in PCT publication WO94/08943 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.) and in Japanese Patent Publication No. Hei 9-2579602 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.), it has not been previously known that 2-amino-1,3-propanediol derivatives having a diaryl sulfide group, which are subjects of the present invention, can serve as an effective immunosuppressor.

DISCLOSURE OF THE INVENTION

[0007] Accordingly, it is an objective of the present invention to provide a diaryl sulfide derivative that exhibits significant immunosuppressive effects with little side effects.

[0008] In the course of studies on immunosuppressive agents that have different mechanisms of action from antimetabolites and calcineurin inhibitors, the present inventors discovered that novel diaryl sulfide derivatives that have a different structure from conventional immunosuppressors exhibit strong immunosuppressive effects. Specifically, the compounds are such that one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other aryl group includes a substituent at its meta-position. This discovery led the present inventors to devise the present invention.

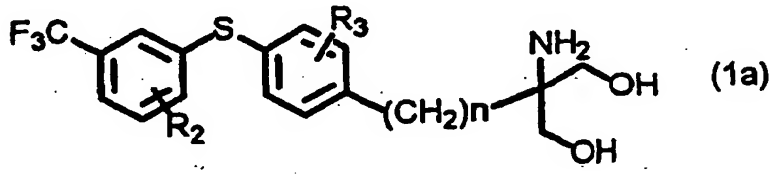
[0009] The present invention thus is an immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1):



wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted

phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxyl having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, or lower alkoxymethyl having 1 to 4 carbon atoms; X is S, SO, or SO_2; and n is an integer from 1 to 4.

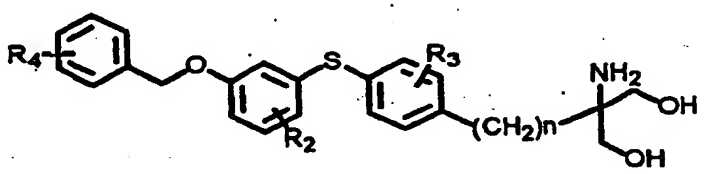
[0010] More specifically, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and n are the same as defined above.

[0011] Furthermore, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and n are the same as defined above; and R_4 is hydrogen, halogen, lower alkyl having 1 to 7 carbon atoms, lower alkoxy having 1 to 4 carbon atoms, or trifluoromethyl.

[0012] The compounds of the general formulae (1), (1a), and (1b) are each a novel compound.

[0013] Examples of the pharmaceutically acceptable salt of the compound of the general formula (1) include acid salts, such as hydrochloride, hydrobromide, acetate, trifluoroacetate, methanesulfonate, citrate, and tartrate.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

Fig. 1 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 2 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 3 is a graph showing activities of a test compound in a mouse skin graft model.

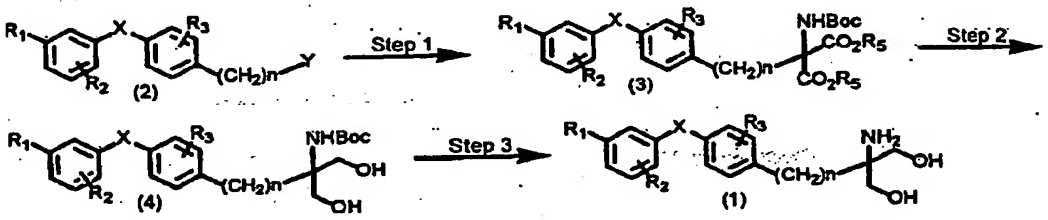
BEST MODE FOR CARRYING OUT THE INVENTION

[0015] With regard to the general formula (1), the term 'halogen atom' encompasses fluorine, chlorine, bromine, and iodine atom. The term 'trihalomethyl group' encompasses trifluoromethyl and trichloromethyl. The phrase 'lower alkyl group having 1 to 7 carbon atoms' encompasses straight-chained or branched hydrocarbons having 1 to 7 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and heptyl. The phrase 'substituted or unsubstituted phenoxy group' encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having

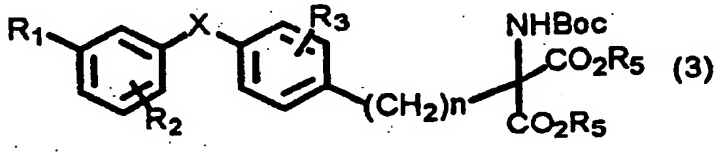
1 to 4 carbon atoms. The term 'aralkyl group' as in 'aralkyl group' or 'aralkyloxy group' encompasses benzyl, diphenylmethyl, phenethyl, and phenylpropyl. The term 'lower alkyl group' as used in 'lower alokoxy group having 1 to 4 carbon atoms,' 'lower alkylthio group having 1 to 4 carbon atoms,' 'lower alkylsulfinyl group having 1 to 4 carbon atoms,' or 'lower alkylsulfonyl group having 1 to 4 carbon atoms,' encompasses straight-chained or branched hydrocarbons having 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, and butyl. The phrase 'substituted or unsubstituted aralkyl group' encompasses those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms.

[0016] According to the present invention, the compounds of the general formula (1) can be produced in the following pathways:

Synthetic Pathway 1

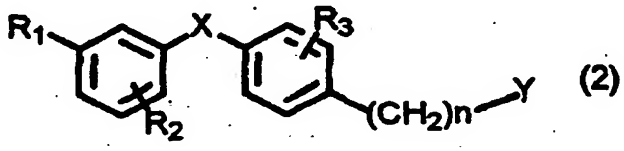


[0017] The compound involved in the synthetic pathway 1 that is represented by the following general formula (3):



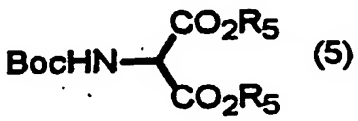
(3)

(wherein R_5 is lower alkyl having 1 to 4 carbon atoms; Boc is *t*-butoxycarbonyl; and R_1, R_2, R_3, X and n are the same as described above) can be prepared by reacting a compound of the following general formula (2):



(2)

(wherein Y is chlorine, bromine, or iodine; and R_1, R_2, R_3, X and n are as described above) with a compound of the following general formula (5):

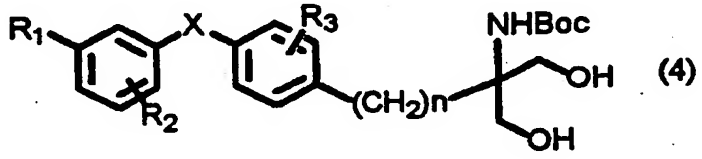


(5)

(wherein R_5 and Boc are as described above) in the presence of a base (Step 1).

[0018] This reaction can be carried out using a reaction solvent such as methanol, ethanol, 1,4-dioxane, dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), or tetrahydrofuran (THF) at a reaction temperature of 0°C to reflux temperature, preferably at a temperature of 80°C to 100°C, in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, and potassium alkoxide.

[0019] The compound involved in the synthetic pathway 1 that is represented by the following general formula (4):

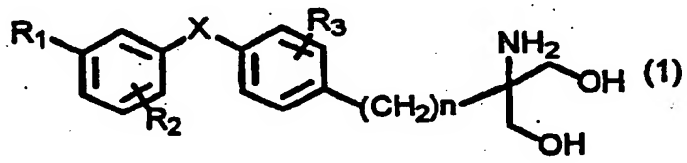


(4)

(wherein R_1, R_2, R_3, X, Boc, and n are as described above) can be prepared by the reduction of the compound of the general formula (3) (Step 2).

[0020] This reaction can be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room temperature, using an alkylborane derivative, such as borane (BH_3) and 9-borabicyclo[3.3.1]nonane (9-BBN), or a metal hydride complex, such as diisobutylaluminum hydride ((iBu)2AlH), sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$), preferably lithium borohydride ($LiBH_4$), and using a reaction solvent such as THF, ethanol and methanol.

[0021] The compound involved in the synthetic pathway 1 that is represented by the general formula (1):

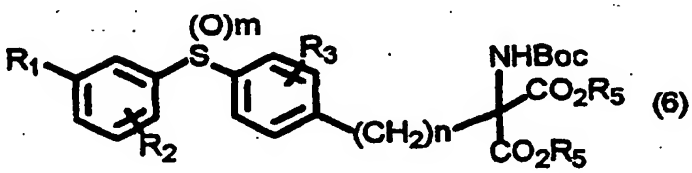


(1)

(wherein R_1, R_2, R_3, X and n are as described above) can be prepared by the acidolysis of the compound of the general formula (4) (Step 3).

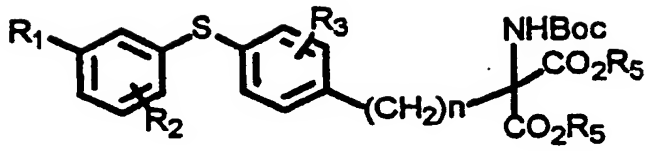
[0022] This reaction can be carried out at a reaction temperature in the range of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid, or in a mixed solvent with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

[0023] Of the compounds of the general formula (3), those in which X is either SO or SO_2, namely, those represented by the following general formula (6):



(6)

(wherein m is an integer of 1 or 2; and R_1, R_2, R_3, R_5, Boc, and n are as described above) may also be prepared by the oxidizing a compound represented by the following general formula (7):

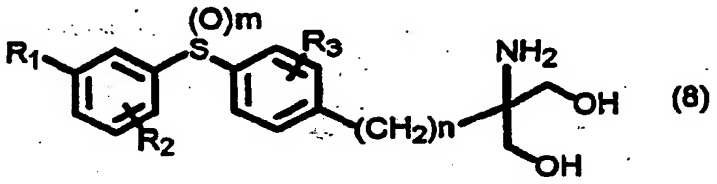


(7)

(wherein R_1, R_2, R_3, R_5, Boc, and n are as described above).

[0024] This reaction can be carried out using a reaction solvent, such as 1,4-dioxane, DMSO, DMF, THF, methylene chloride or chloroform, along with an oxidizing agent, such as potassium permanganate, m-chloroperbenzoic acid or aqueous hydrogen peroxide, at a reaction temperature of 0°C to reflux temperature, preferably at room temperature.

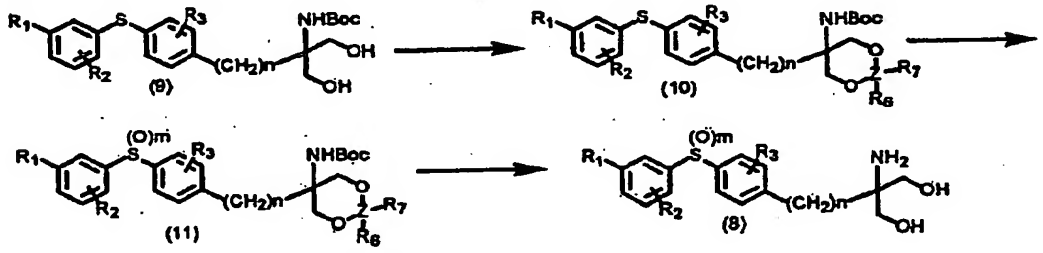
[0025] Of the compounds of the general formula (1), those in which X is either SO or SO_2, namely, those represented by the following general formula (8)):



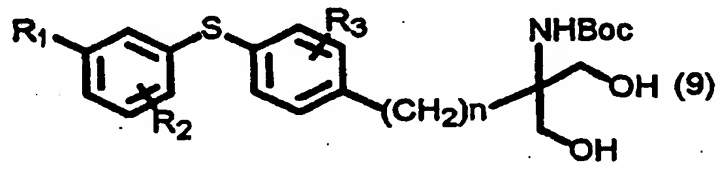
(8)

(wherein R_1, R_2, R_3, Boc, m, and n are as described above) may also be prepared by the following synthetic pathway:

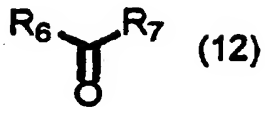
Synthetic pathway 2



[0026] Specifically, a compound represented by the following general formula (9):

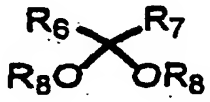


(wherein R_1, R_2, R_3, Boc, and n are as described above) can be reacted either with a compound represented by the following general formula (12):



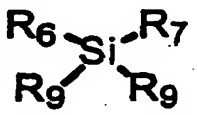
(12)

(wherein R_6 and R_7 each independently represent hydrogen or lower alkyl having 1 to 4 carbon atoms), or with a compound represented by the following general formula (13):



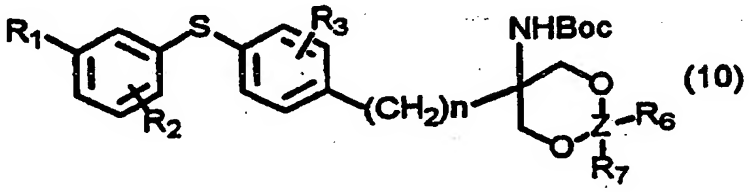
(13)

(wherein R_8 is lower alkyl having 1 to 4 carbon atoms; and R_6 and R_7 are as described above), or with a compound represented by the following general formula (14):



(14)

(wherein R_9 is chlorine or trifluoromethanesulfonyloxy; and R_6 and R_7 are as described above) to produce a compound represented by the following general formula (10):



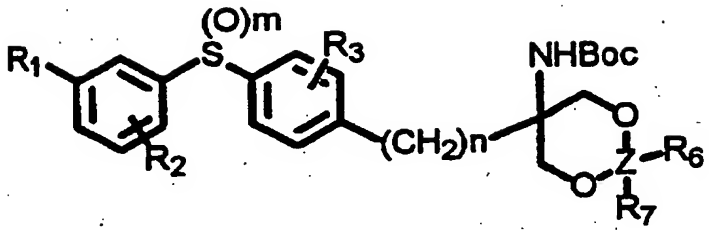
(10)

(whrein Z is carbon or silicon; and R_1, R_2, R_3, R_6, R_7, Boc, and n are as described above).

[0027] The reaction between the compound of the general formula (9) and the compound of the general formula (12) or the compound of the general formula (13) can be carried out at a reaction temperature in the range of room temperature to 100°C either in the presence of a Lewis acid such as zinc chloride or in the presence of an acid catalyst such as camphorsulfonic acid, paratoluenesulfonic acid, and pyridinium paratoluenesulfonic acid, and may be carried out either in the absence of solvent or in the presence of a reaction solvent such as DMF, THF, and methylene chloride.

[0028] The reaction between the compound of the general formula (9) and the compound of the general formula (14) can be carried out at a reaction temperature of 0°C to 100°C in the presence of a base, such as triethylamine, pyridine, 2,6-lutidine, and imidazole, and can be carried out using a reaction solvent such as DMF, THF, methylene chloride, chloroform, and acetonitrile.

[0029] The compound involved in the synthetic pathway 2 that is represented by the following general formula (11):



(11)

(wherein R_1, R_2, R_3, R_6, R_7, Z, Boc, m and n are as described above) can be prepared by the oxidizing the compound of the general formula (10).

[0030] This reaction can be carried out using a reaction solvent, such as 1,4-dioxane, DMSO, DMF, THF, methylene chloride or chloroform, along with an oxidizing agent, such as potassium permanganate, m-chloroperbenzoic acid or aqueous hydrogen peroxide, at a reaction temperature of 0°C to reflux temperature, preferably at room temperature.

[0031] The compound of the general formula (8) involved in the synthetic pathway 2 can be prepared by the acidolysis, or desilylation followed by acidolysis, of the compound of the general formula (11).

[0032] This reaction can be carried out at a reaction temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, trifluoroacetic acid, or in a mixed solution with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

[0033] When Z in the general formula (11) is a silicon atom, the compound of the general formula (11) may also be synthesized by a reaction with potassium fluoride, cesium fluoride, or tetrabutylammonium fluoride, carried out at a temperature of 0°C to room temperature in a solvent such as THF, DMF, 1,4-dioxane, followed by the above-described acidolysis.

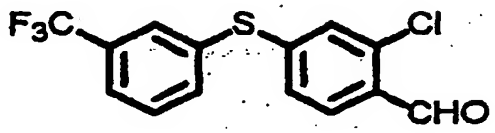
Examples

[0034] The present invention will now be described with reference to examples, which are provided by way of example only and are not intended to limit the scope of the invention in any way.

<Reference Example 1>

2-chloro-4-[(3-trifluoromethyl)phenylthio]benzaldehyde

[0035]

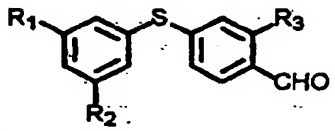


[0036] Potassium carbonate (2.76g) was added to a solution of 2-chloro-4-fluorobenzaldehyde (1.15g) and 3-(trifluoromethyl)thiophenol (1.33g) in DMF (20mL) and the mixture was stirred for 1 hour while heated to 120°C. The reaction mixture was poured into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired product (1.96g) was obtained as a pale yellow oil.

<Reference Examples 2 through 9>

[0037] Using various thiophenols and aldehydes, the compounds shown in Table 1 below were each synthesized in the same manner as described above.

Table 1

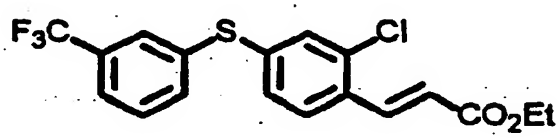


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
2	CF_3	H	H	6	MeO	H	H
3	CF_3	H	CF_3	7	MeO	H	Cl
4	CF_3	CF_3	H	8	MeO	H	CF_3
5	CF_3	CF_3	Cl	9	Cl	Cl	H

<Reference Example 10>

Ethyl 2'-chloro-4'-[(3-trifluoromethyl)phenylthio]cinnamate

[0038]

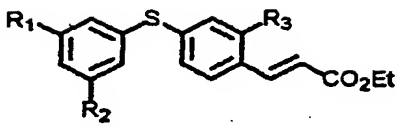


[0039] Under argon, 60% sodium hydride (272mg) was added to a solution of ethyl (diethylphosphono)acetate (1.35mL) in THF (30ml) at 0°C and the mixture was stirred for 30 minutes. A solution of the compound of Reference Example 1 (1.96g) in THF (15mL) was then added dropwise. With the temperature maintained, the mixture was further stirred for 2 hours, followed by addition of water and then extraction with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired product (1.72g) was obtained as a colorless oil.

<Reference Examples 11 through 18>

[0040] Using the compounds of Reference Examples 2 through 9, the compounds shown in Table 2 below were each synthesized in the same manner as described above.

Table 2

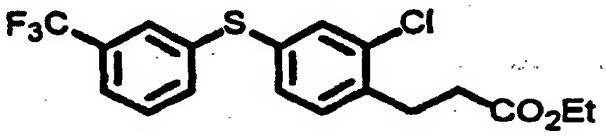


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
11	CF_3	H	H	15	MeO	H	H
12	CF_3	H	CF_3	16	MeO	H	Cl
13	CF_3	CF_3	H	17	MeO	H	CF_3
14	CF_3	CF_3	Cl	18	Cl	Cl	H

<Reference Example 19>

Ethyl 2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamate

[0041]

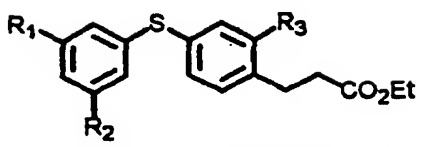


[0042] The compound of Reference Example 10 (1.72g) was dissolved in ethanol (70mL). Bismuth chloride (703mg) was then added to the solution while the solution was stirred at 0°C. To the resulting mixture, sodium borohydride (673mg) was added in small portions, and the mixture was stirred for 1 hour at the same temperature and subsequently for 3 hours at room temperature. Ice water was then added to the reaction mixture and the crystallized inorganic deposits were filtered out through celite. The filtrate was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure. In this manner, the desired product (1.50g) was obtained as a colorless oil.

<Reference Examples 20 through 25>

[0043] Using the compounds of Reference Examples 11, 12, and 14 through 17, the compounds shown in Table 3 below were each synthesized in the same manner as described above.

Table 3

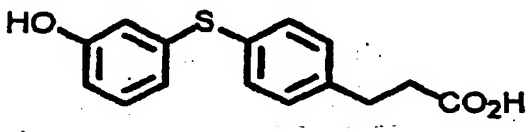


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
20	CF_3	H	H	23	MeO	H	H
21	CF_3	H	CF_3	24	MeO	H	Cl
22	CF_3	CF_3	Cl	25	MeO	H	CF_3

<Reference Example 26>

4'-(3-hydroxyphenylthio)dihydrocinnamic acid

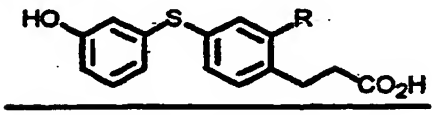
[0044]



[0045] Under argon, a 1mol/L solution of boron tribromide in methylene chloride (20mL) was added to a solution of the compound of Reference Example 23 (3.20g) in methylene chloride (50mL), and the mixture was stirred for 8 hours until room temperature. Water was then added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water, a saturated aqueous solution of sodium bicarbonate, and a saturated aqueous solution of sodium chloride, and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 2:1). In this manner, the desired product (2.00g) was obtained as a colorless powder.

<Reference Examples 27 and 28>

[0046] Using the compounds of Reference Examples 24 and 25, the compounds shown below were each synthesized in the same manner as in Reference Example 26.

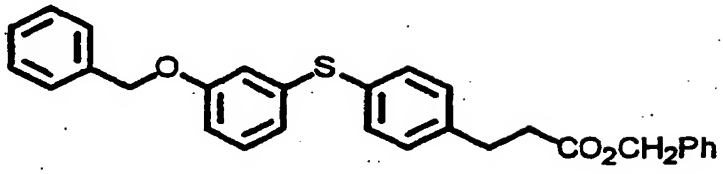


Reference Example	R	Reference Example	R
27	Cl	28	CF_3

<Reference Example 29>

Benzyl 4'-(3-benzyloxyphenylthio)dihydrocinnamate

[0047]

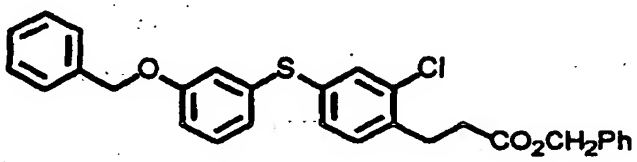


[0048] The compound of Reference Example 26 (2.00g) was dissolved in DMF (30mL), and benzyl bromide (2.4mL) and potassium carbonate (2.00g) were added to the solution. The mixture was stirred at 60°C for 2 hours. Water was then added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (2.29g) was obtained as a colorless oil.

<Reference Example 30>

Benzyl 4'-(3-benzyloxyphenylthio)-2'-chlorodihydrocinnamate

[0049]

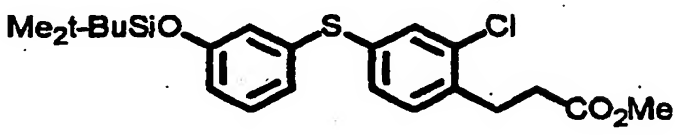


[0050] Using the compound of Reference Example 27, the reaction was carried out in the same manner as in Reference Example 29 to obtain the desired product as a yellow oil.

<Reference Example 31>

Methyl 4'-[(3-*t*-butyldimethylsiloxy)phenylthio]-2'-chlorodihydrocinnamate

[0051]



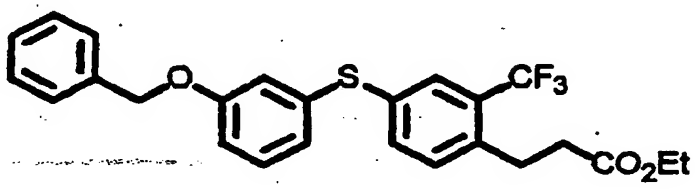
[0052] To a methanol solution (70mL) of the compound of Reference Example 27 (6.20g), thionyl chloride (2.2mL) was added dropwise and the mixture was refluxed for 1 hour. The solvent was removed by distillation under reduced pressure to obtain a methyl ester as a colorless oil (5.80g). The resulting ester (5.80g) was dissolved in DMF (80mL)

to form a solution. To this solution, imidazole (1.57g) and *t*-butyldimethylchlorosilane (3.47g) were added at 0°C and the mixture was stirred for 7 hours until room temperature was reached. Subsequently, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (7.26g) was obtained as a colorless oil.

<Reference Example 32>

Ethyl 4'-(3-benzyloxyphenylthio)-2'-trifluoromethyldihydrocinnamate

[0053]

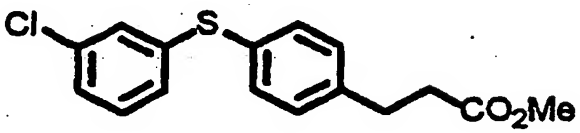


[0054] Using ethanol, the compound of Reference Example 28 was subjected to the same process as that of Reference Example 31 to synthesize an ethyl ester, which in turn was subjected to the same process as that of Reference Example 29 to obtain a pale yellow oil.

<Reference Example 33>

Ethyl 4'-(3-chlorophenylthio)dihydrocinnamate

[0055]

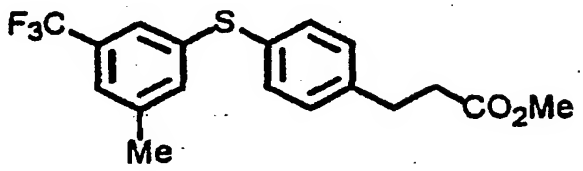


[0056] Under argon, the compound of Reference Example 18 (3.60g) was dissolved in methanol (50mL). Magnesium (500mg) was then added to the solution while the solution was stirred at 10°C. The solution was stirred for another 1 hour at this temperature, followed by addition of magnesium (250mg) and further stirring for 3 hours. Subsequently, diluted hydrochloric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (3.13g) as a pale yellow oil.

<Reference Example 34>

Methyl 4'-(3-trifluoromethyl-5-methylphenylthio)dihydrocinnamate

[0057]

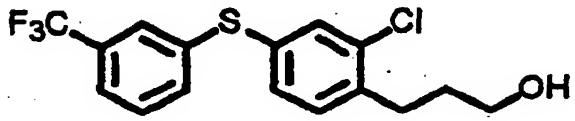


[0058] Using the compound of Reference Example 13, the reaction was carried out in the same manner as in Reference Example 33 to obtain the desired product as a colorless oil.

<Reference Example 35>

2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamyl alcohol

[0059]

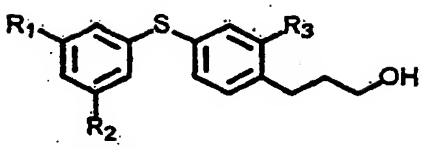


[0060] The compound of Reference Example 19 (1.50g) was dissolved in THF (30mL). Lithium aluminum hydride (200mg) was then added to the solution while the solution was stirred at 0°C. After 30 minutes, a 20% NaOH solution was added and the crystallized inorganic deposits were removed by filtration through celite. The filtrate was extracted with ethyl acetate and the organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (1.38g) as a colorless oil.

<Reference Examples 36 through 45>

[0061] Using the compounds of Reference Examples 20 through 22, 24, and 29 through 34, the reactions were carried out in the same manner as in Reference Example 35 to synthesize the compounds shown in Table 4 below.

Table 4

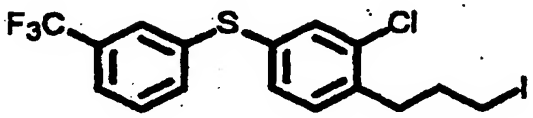


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
36	CF_3	H	H	41	$PhCH_2O$	H	H
37	CF_3	H	CF_3	42	$PhCH_2O$	H	Cl
38	CF_3	CF_3	Cl	43	$PhCH_2O$	H	CF_3
39	CF_3	Me	H	44	t-$BuMe_2SiO$	H	Cl
40	MeO	H	Cl	45	Cl	H	H

<Reference Example 46>

2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamyl iodide

[0062]

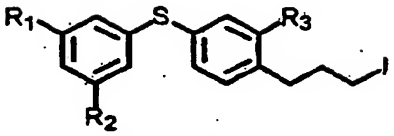


[0063] The compound of Reference Example 35 (1.38g) was dissolved in THF (20mL). Imidazole (545mg), triphenylphosphine (2.10g) and iodine (2.00g) were added to the solution while the solution was stirred at 0°C. The reaction mixture was further stirred for 2 hours at this temperature and another 1.5 hours at room temperature, followed by the addition of imidazole (160mg), triphenylphosphine (600mg) and iodine (500mg). The mixture was subsequently stirred overnight. Water and then sodium thiosulfate were added to the reaction mixture, followed by extraction with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 50:1). In this manner, the desired product (1.55g) was obtained as a colorless oil.

<Reference Examples 47 through 56>

[0064] Using the compounds of Reference Examples 36 through 45, the reactions were carried out in the same manner as in Reference Example 46 to synthesize the compounds shown in Table 5 below.

Table 5

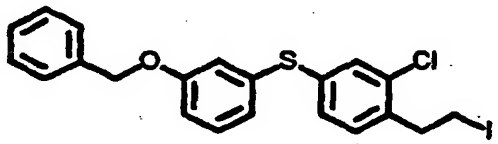


Reference Example	R1	R2	R3	Reference Example	R1	R2	R3
47	CF_3	H	H	52	$PhCH_2O$	H	H
48	CF_3	H	CF_3	53	$PhCH_2O$	H	Cl
49	CF_3	CF_3	Cl	54	$PhCH_2O$	H	CF_3
50	CF_3	Me	H	55	$t\text{-}BuMe_2SiO$	H	Cl
51	MeO	H	Cl	56	Cl	H	H

<Reference Example 57>

4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl iodide

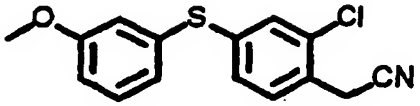
[0065]



<Reference Example 57-1>

2'-chloro-4'-(3-methoxyphenylthio)benzyl cyanide

[0066]

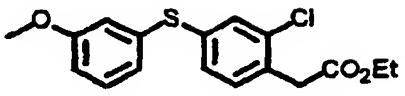


[0067] The compound of Reference Example 7 was treated in the same manner as in Reference Example 35 to obtain an alcohol. The alcohol (5.64g) was dissolved in methylene chloride (100mL) and phosphorus tribromide (2.25mL) was added dropwise. The mixture was stirred at room temperature for 1 hour, followed by addition of ice water and extraction with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation to obtain a pale yellow oil. The oil and potassium cyanide (1.56g) were dissolved in a mixed solvent of DMSO (25mL) and water (10mL) and the solution was stirred at 90°C for 5 hours. Water was then added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired cyanide form (3.81g) was obtained as a pale yellow oil.

<Reference Example 57-2>

Ethyl 2'-chloro-4'-(3-methoxyphenylthio)phenylacetate

[0068]

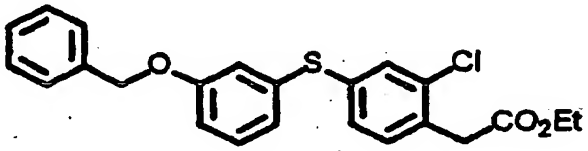


[0069] The above cyanide (3.81g) and potassium hydroxide (3.68g) were dissolved in a mixed solvent of ethanol (80mL) and water (10mL) and the solution was refluxed for 6 hours. The solution was then allowed to cool and the insoluble deposits were removed by filtration. The filtrate was neutralized with diluted hydrochloric acid and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation and ethanol (50mL) and thionyl chloride (2mL) were added to the resulting residue. The mixture was stirred at room temperature for 1 hour and the solvent was removed by distillation. The resulting residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1). In this manner, the desired ethyl ester form (3.89g) was obtained as a colorless oil.

<Reference Example 57-3>

Ethyl 4'-(3-benzyloxyphenylthio)-2'-chlorophenyl acetate

[0070]



[0071] The desired ethyl ester was treated in the same manner as in Reference Example 26 and then in the same manner as in Reference Example 57-2 to form an ethyl ester, which in turn was subjected to the same process as that of Reference Example 29 to obtain a benzyl ether.

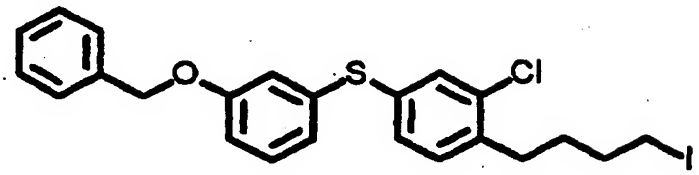
4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl Iodide

[0072] The compound of Reference Example 57-3 was used as the starting material and was subjected to the same process as that of Reference Example 35 to obtain 4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl alcohol, which in turn was subjected to the same process as that of Reference Example 46 to obtain the desired product as a colorless oil.

<Reference Example 58>

1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutyl benzene

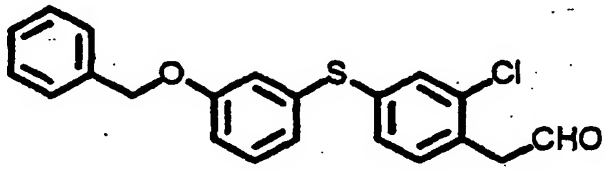
[0073]



<Reference Example 58-1>

4-(3-benzyloxyphenylthio)-2-chlorophenethylaldehyde

[0074]

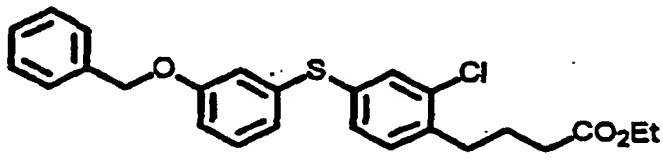


[0075] The compound of Reference Example 57-3 was subjected to alkaline hydrolysis and then to condensation with N,O-dimethylhydroxyamine to form an amid, which in turn was reduced in the same manner as in Reference Example 35 to obtain the aldehyde as a yellow oil.

<Reference Example 58-2>

Ethyl 4-[(3-benzyloxyphenylthio)-2-chlorophenyl]butyric acid

[0076]



[0077] The compound of Reference Example 58-1 was treated in the same manner as in Reference Example 10 and then in the same manner as in Reference Example 19 to obtain the desired ethyl butyrate derivative.

1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutylbenzene

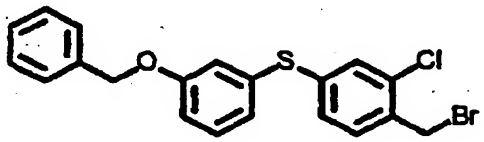
[0078] The compound of Reference Example 58-2 was used as the starting material and was subjected to the same

process as that of Reference Example 57 to obtain the desired product as a colorless oil.

<Reference Example 59>

4'-(3-benzyloxyphenylthio)-2'-chlorobenzyl bromide

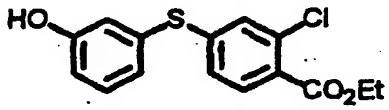
[0079]



<Reference Example 59-1>

Ethyl 2-chloro-4-(3-hydroxyphenylthio)benzoate

[0080]



[0081] 2-chloro-4-fluorobenzonitrile, in place of 2-chloro-4-fluorobenzaldehyde, was used in the same process as that of Reference Example 1 to obtain 2-chloro-4-(3-methoxyphenylthio)benzonitrile, which in turn was hydrolyzed in the same manner as in Reference Example 57-2. Then, in the same fashion as in Reference Example 26, methoxy group was removed from the reaction product and the product was subjected to esterification to obtain the desired product as a yellow oil.

<Reference Example 59-2>

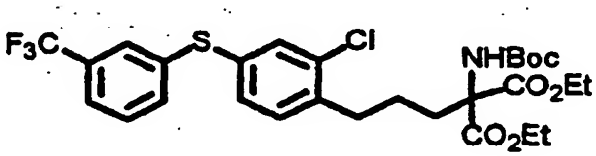
4'-(3-benzyloxyphenylthio)-2'-chlorobenzyl bromide

[0082] The compound of Reference Example 59-1 was subjected to the same process as that of Reference Example 29 to obtain a benzyl ether, which in turn was treated in the same manner as in Reference Example 35 to form an alcohol. Subsequently, using carbon tetrabromide in place of iodine, the reaction product was treated in the same manner as in Reference Example 46. In this manner, the desired product was obtained as a colorless oil.

<Example 1>

Ethyl 2-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-trifluoromethylphenylthio)]phenyl-2-ethoxycarbonylpentanoate

[0083]



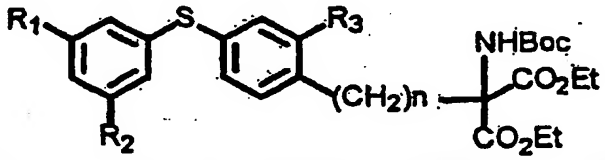
[0084] Under argon and at room temperature, sodium-*t*-butoxide (490mg) was added to diethyl 2-*t*-butoxycarbonylaminomalonate (1.3mL) dissolved in a mixed solvent of THF (35mL) and DMF (4mL). The mixture was then stirred at 80°C for 20 minutes and was allowed to cool to room temperature. A solution of the compound of Reference Example 46 (1.55g) in THF (5mL) was added to the mixture. Subsequently, the mixture was refluxed for 5 hours and was then poured into ice water. The resulting mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (1.87g) was obtained as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.22-1.36(6H, m), 1.42(9H, s), 1.45-1.53(2H, m), 2.37(2H, br), 2.74(2H, t, J=7.8Hz), 4.23 (4H, m), 5.94(1H, s), 7.16-7.21(2H, m), 7.36-7.56(5H, m)

<Examples 2 through 13>

[0085] Using the compounds of Reference Examples 47 through 58, the reactions were carried out in the same manner as in Example 1 to synthesize the compounds shown in Table 6 below:

Table 6



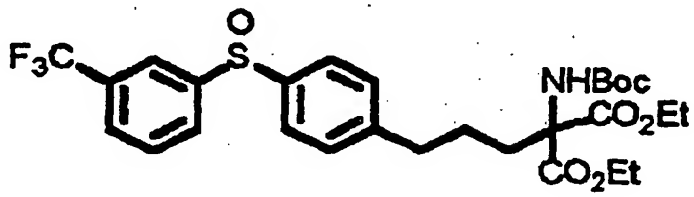
Example	R1	R2	R3	n	Yield (%)	Characteristics
2	CF_3	H	H	3	90	Colorless oil
3	CF_3	H	CF_3	3	53	Paleyellow oil
4	CF_3	CF_3	Cl	3	66	Colorless oil
5	CF_3	Me	H	3	100	Colorless oil
6	MeO	H	Cl	3	87	Colorless oil
7	$PhCH_2O$	H	H	3	-	Colorless oil
8	$PhCH_2O$	H	Cl	2	100	Paleyellow oil
9	$PhCH_2O$	H	Cl	3	100	Colorless oil
10	$PhCH_2O$	H	Cl	4	100	Colorless oil
11	$PhCH_2O$	H	CF_3	3	100	Colorless oil
12	t-$BuMe_2SiO$	H	Cl	3	-	Colorless oil
13	Cl	H	H	3	82	Colorless oil

The mark "-" means yield is shown in Table 7 as a total yield.

<Example 14>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-trifluoromethylphenylsulfinyl)]phenylpentanoate

[0086]



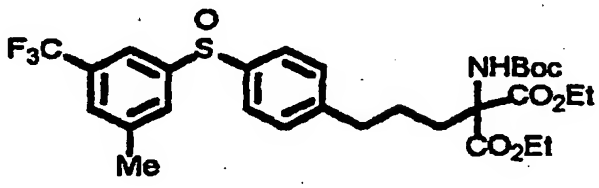
[0087] The compound of Example 2 (1.50g) was dissolved in methylene chloride (80mL) and, while the solution was stirred at 0°C, m-chloroperbenzoic acid (450mg) was added in small portions. The resulting mixture was stirred for 1 hour at the same temperature and then another 2 hours at room temperature, followed by the addition of water. The resulting mixture was extracted with ethyl acetate. The organic phase was sequentially washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1). In this manner, the desired product (1.10g) was obtained as a colorless oil.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18-1.21(6H, m), 1.40(9H, s), 1.44-1.52(2H, m), 2.30(2H, br), 2.66(2H, t, J=7.3Hz), 4.14-4.22(4H, m), 5.91(1H, br), 7.27(2H, d, J=8.3Hz), 7.56(2H, d, J=8.3Hz), 7.59(1H, t, J=8.3Hz), 7.69(1H, d, J=8.3Hz), 7.78(1H, d, J=8.3Hz), 7.95(1H, s)

<Example 15>

Ethyl 2-*t*-butoxycarbonylamino-5-[4-(3-trifluoromethyl-5-methylphenylsulfinyl)]phenyl-2-ethoxycarbonylpentanoate

[0088]



[0089] Using the compound of Example 5, the reaction was carried out in the same manner as in Example 14 to obtain the desired product as a colorless oil.

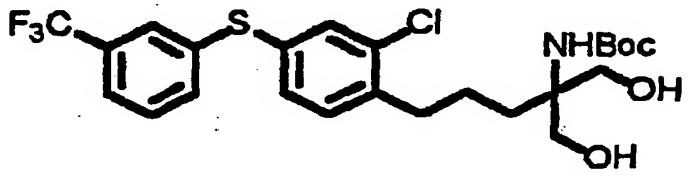
FABMS : 600 ([M+H]+)

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18-1.22(6H, m), 1.41(9H, s), 1.46-1.50(2H, m), 2.31(2H, br), 2.45(3H, s), 2.66(2H, t, J=7.3Hz), 4.14-4.22(4H, m), 5.92(1H, br s), 7.27(2H, d, J=7.8Hz), 7.48(1H, s), 7.55(2H, d, J=7.8Hz), 7.62(1H, s), 7.70 (1H, s)

<Example 16>

2-*t*-butoxycarbonylamino-2-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol

[0090]

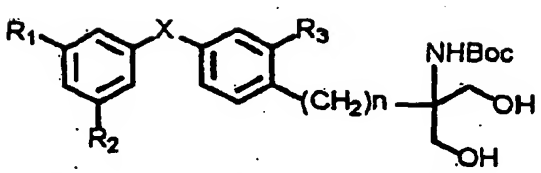


[0091] The compound of Example 1 (1.87g) was dissolved in THF (30mL) and lithium borohydride (675mg) was added to the solution while the solution was stirred at 0°C. Subsequently, ethanol (5mL) was added to the solution and the mixture was stirred overnight while allowed to gradually warm to room temperature. Ice water was then added to the reaction mixture and the organic solvent was removed by distillation under reduced pressure. 10% aqueous citric acid was added to the residue to adjust the pH to 3 and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1) to obtain the desired product (1.10g) as a colorless oil.
FABMS : 520 ([M+H]+)
^{1}H-NMR(400MHz, $CDCl_3$) δ 1. 43 (9H, s), 1.62-1.65(4H, m), 2.72(2H,br), 3.31(2.H, br), 3.57-3.62(2H, m), 3.81-3.85 (2H, m), 4.93(1H, s), 7.20-7.27(3H, m), 7.38-7.55(4H, m)

<Examples 17 through 30>

[0092] Using the compounds of Examples 2 through 15, the reactions were carried out in the same manner as in Example 16 to synthesize the compounds shown in Table 7 below.

Table 7



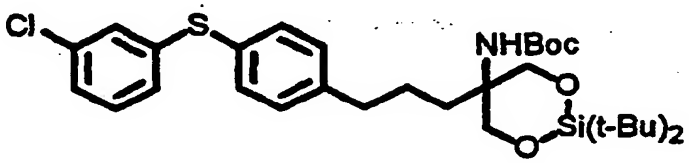
Example	R1	R2	R3	X	n	Yield(%)	Characteristics
17	CF_3	H	H	S	3	89	Colorless powder
18	CF_3	H	H	SO	3	71	Colorless amorphous
19	CF_3	H	CF_3	S	3	51	Colorless oil
20	CF_3	CF_3	Cl	S	3	66	Colorless amorphous
21	CF_3	Me	H	S	3	81	Colorless powder
22	CF_3	Me	H	SO	3	65	Colorless powder
23	MeO	H	Cl	S	3	56	Colorless oil
24	$PhCH_2O$	H	H	S	3	(45)	Colorless oil
25	$PhCH_2O$	H	Cl	S	2	41	Colorless oil
26	$PhCH_2O$	H	Cl	S	3	65	Colorless oil
27	$PhCH_2O$	H	Cl	S	4	76	Colorless oil
28	$PhCH_2O$	H	CF_3	S	3	66	Colorless oil
29	t-$BuMe_2SiO$	H	Cl	S	3	(33)	Colorless oil
30	Cl	H	H	S	3	41	Colorless oil

In the parentheses, shown is the total yield of the two steps.

<Example 31>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[(3-chlorophenylthio)phenyl]propyl-1,3,2-dioxasilane

[0093]

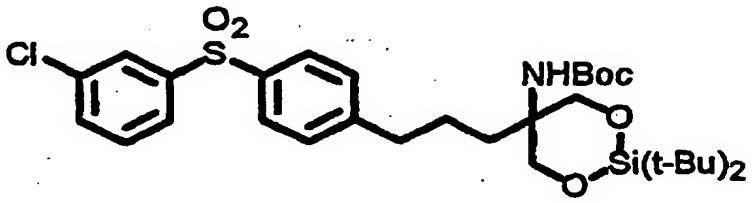


[0094] At 0°C, di-*t*-butylsilyl bis(trifluoromethanesulfonate) (0.55mL) was added to a DMF solution (15mL) containing the compound of Example 30 (490mg) and 2,6-lutidine (0.35mL). The mixture was stirred for 5 hours until room temperature and was poured into ice water. The mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 8:1) to obtain the desired product (630mg) as a colorless powder. ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05(9H, s), 1.06(9H, s), 1.43(9H, s), 1.57-1.62(4H, m), 2.58(2H, br), 3.89(2H, d, J=10.7Hz), 4.22(2H, d, J=10.7Hz), 4.92(1H, br s), 7.09-7.20(6H, m), 7.34(2H, d, J=8.3Hz)

<Example 32>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[(3-chlorophenylsulfonyl)phenyl]propyl-1,3,2-dioxasilane

[0095]



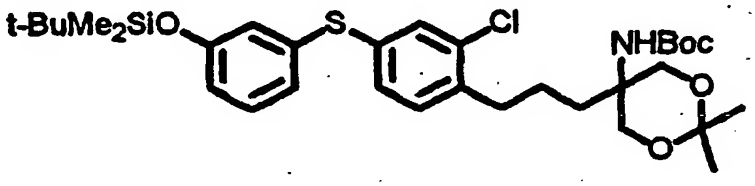
[0096] The compound of Example 31 was oxidized in the same manner as in Example 14 to obtain the desired product as a colorless powder.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04(9H, s), 1.05(9H, s), 1.41(9H, s), 1.55-1.57(4H, m), 2.63(2H, br), 3.86(2H, d, J=11.2Hz), 4.19(2H, d, J=11.2Hz), 4.92(1H, br), 7.29(2H, d, J=8.3Hz), 7.44(1H, t, J=8.3Hz), 7.50-7.53(1H, m), 7.80-7.85(1H, m), 7.84(2H, d, J=8.3Hz), 7.91-7.92(1H, m)

<Example 33>

5-*t*-butoxycarbonylamino-5-[4-(3-*t*-butoxydimethylsiloxyphenylthio)-2-chlorophenyl]propyl-2,2-dimethyl-1,3-dioxane

[0097]

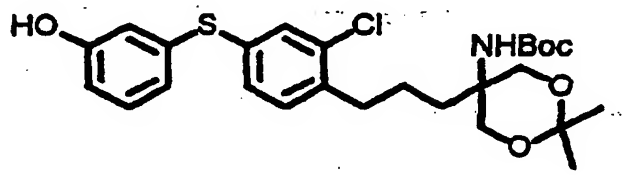


[0098] To a solution of the compound of Example 29 (1.88g) in DMF (30mL), 2,2-dimethoxypropane (2.5mL) along with p-toluenesulfonic acid (100mg) was added and the mixture was stirred for 5 hours while heated at 80°C. The reaction mixture was poured into water and was extracted with ethyl acetate. The organic phase was then sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (1.11g) as a colorless powder.

<Example 34>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-hydroxyphenylthio)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0099]

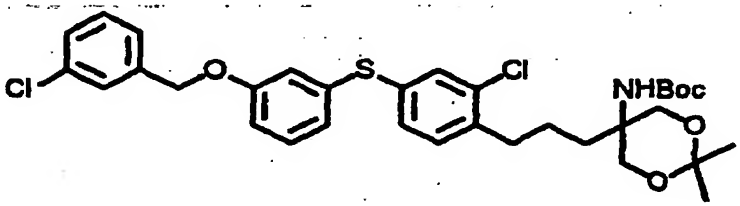


[0100] To a solution of the compound of Example 33 (1.10g) in THF (20mL), a 1mol/L solution of tetrabutylammonium fluoride in THF (5mL) was added. After 10 minutes, the reaction mixture was poured into water and was extracted with ethyl acetate.
The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (900mg) as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.39(9H, s), 1.40(3H, s), 1.41(3H, s), 1.60(4H, br s), 2.78(2H, br s), 3.64(2H, d, J=11.7Hz), 3.83(2H, d, J=11.7Hz), 4.89(1H,br), 7.27(1H, br), 6.53(1H, br), 6.65(1H, d, J=6.9Hz), 6.85(1H, d,J=8.3Hz), 7.11-7.16 (2H, m), 7.26-7.28(1H, m), 7.45(1H, br s)

<Example 35>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-(3-chlorobenzyloxy)phenylthio)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0101]

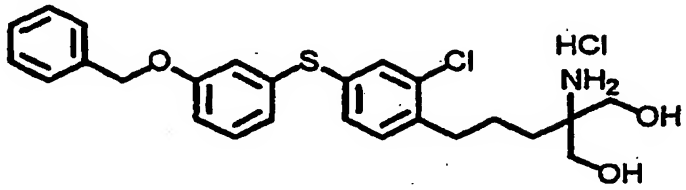


[0102] To a solution of the compound of Example 34 (500mg) in DMF (10mL), potassium carbonate (500mg) and m-chlorobenzyl bromide (0.16mL) were added and the mixture was stirred at 70°C for 1 hour. The reaction mixture was then poured into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (520mg) as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.41(3H, s), 1.42(12H, s), 1.53-1.56(2H, m), 1.76(2H, br), 2.69(2H, t, J=7.8Hz), 3.65(2H, d, J=11.7Hz), 3.88(2H, d, J=11.7Hz), 4.88(1H, br), 4.99(2H, s), 6.86(1H, dd, J=8.3, 2.0Hz), 6.92-6.95(2H, m), 7.11-7.16 (2H, m), 7.21-7.32(5H, m), 7.40(1H, s)

<Example 36>

2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propanediol hydrochloride

[0103]



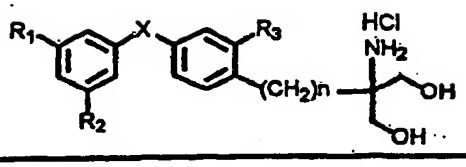
[0104] Ethyl acetate (100mL) containing 3mol/L hydrochloric acid was added to a methanol solution (150mL) of the compound of Example 26 (6.91g) and the mixture was stirred at room temperature for 1 hour. The solvent was removed by distillation under reduced pressure. A mixture of methylene chloride and hexane (methylene chloride:hexane = 1:5) was added to the residue and the resultant crystals were collected by filtration. After drying, the desired product (5.75g) was obtained as a colorless powder.
FABMS: 458([M+H]+)
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.57(4H, br s), 2.64(2H, br s), 3.36-3.46(4H, m), 5.09(2H, s), 5.31(2H, t, J=4.9Hz), 6.89(1H, d, J=8.3Hz), 6.95(1H, t, J=2.0Hz), 6.99(1H, dd, J=8.3Hz, 2.0Hz), 7.23(1H, dd, J=7.8Hz, 2.0Hz), 7.29(8H, m), 7.70(3H, br s) Melting point = 132-133°C (EtOH-iPr_2O)

Elemental analysis (%): $C_{25}H_{28}ClNO_3S$·HCl			
	C	H	N
Calcd.	60.72	5.91	2.83
Found	60.71	5.85	2.91

<Examples 37 through 45>

[0105] Using the compounds of Examples 16 through 24, the reactions were carried out in the same manner as in Example 36 to synthesize the compounds shown in Table 8 below.

Table 8

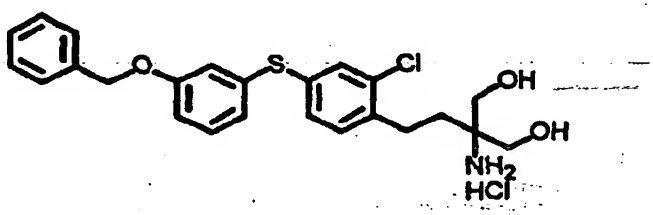


Example	R1	R2	R3	X	n	Yield(%)	Characteristics	FABMS [M+H]+	Melting point °C
37	CF_3	H	H	S	3	94	Colorless powder	386	140-143
38	CF_3	H	H	SO	3	97	Colorless amorphous	402	
39	CF_3	H	Cl	S	3	93	Colorless powder	420	194-197
40	CF_3	H	CF_3	S	3	83	Colorless powder	453	107-112
41	CF_3	CF_3	Cl	S	3	93	Colorless powder	488	159-162
42	CF_3	Me	H	S	3	86	Colorless powder	400	117-119
43	CF_3	Me	H	SO	3	88	Colorless amorphous	416	
44	MeO	H	Cl	S	3	90	Yellow powder	382	98-100
45	$PhCH_2O$	H	H	S	3	100	Colorless powder	424	97-100

<Example 46>

2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol hydrochloride

[0106]



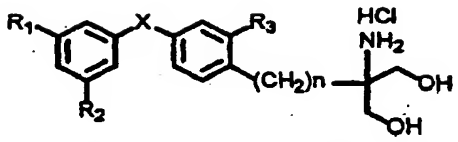
[0107] Using the compound of Example 25, the reaction was carried out in the same manner as in Example 36 to obtain the desired product.
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.75-1.79(2H, m), 2.69-2.73(2H, m), 3.54(2H, s), 5.10(2H, s), 5.40(2H, t, J=4.0Hz), 6.91(1H, dd, J=8.3Hz, 1.8Hz), 6.96(1H, t, J=1.8Hz), 7.00(1H, dd, J=8.3Hz, 1.8Hz), 7.26(1H, dd, J=8.8Hz, 1.8Hz), 7.30-7.42(8H, m), 7.82(3H, br)
FABMS: 444([M+H]+) Melting point = 143-145°C (EtOH-iPr_2O)

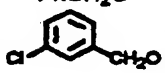
Elemental analysis (%): $C_{24}H_{26}ClNO_3S$·HCl			
	C	H	N
Calcd.	60.00	5.66	2.92
Found	59.88	5.61	2.97

<Examples 47 through 51>

[0108] Using the compounds of Examples 27, 28, 30, 32, and 35, the reactions were carried out in the same manner as in Example 36 to synthesize the compounds shown in Table 9 below.

Table 9



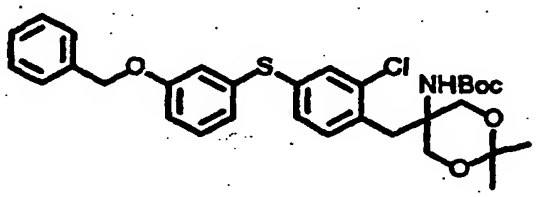
Example	R1	R2	R3	X	n	Yield(%)	Characteristics	FABMS [M+H]*	Melting point °C
47	$PhCH_2O$	H	Cl	S	4	88	Colorless powder	472	91-93
48	$PhCH_2O$	H	CF_3	S	3	85	Colorless powder	492	86-98
49		H	Cl	S	3	100	Colorless powder	492	95-98
50	Cl	H	H	S	3	77	Colorless powder	352	122-125
51*	Cl	H	H	SO_2	3	97	Colorless powder	384	171-174

* Carried out after Bu_4NF treatment.

<Example 52>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-benzyloxyphenylthio)phenyl]methyl-2,2-dimethyl-1,3-dioxane

[0109]

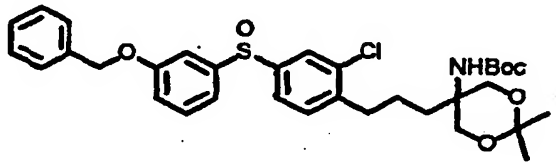


[0110] Using the compound of Reference Example 59, the reaction was carried out in the same manner as in Example 1 to synthesize an ester, which in turn was subjected to the same process as that of Reference Example 16 to be converted to a diol. Subsequently, the diol was treated in the same manner as in Example 35 to obtain the desired product as a yellow oil. ^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(6H, s), 1.46(9H, s), 3.23(2H, s), 3.83(2H, d, J=11.7Hz), 3.89 (2H, d, J=11.7Hz), 4.84(1H, br s), 5.03(2H, s), 6.91(1H, ddd, J=8.3Hz, 2.4Hz, 1.0Hz), 6.95-6.99(2H, m), 7.12(1H, dd, J=8.3Hz, 2.0Hz), 7.22-7.41(8H, m)

<Example 53>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-benzyloxyphenylsulfinyl)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0111]

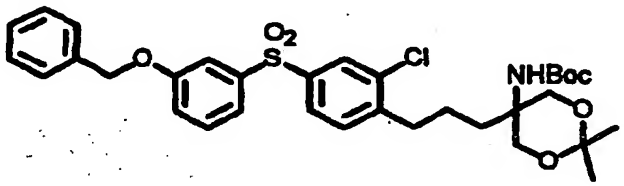


[0112] The compound of Example 26 was subjected to the reaction in the same manner as in Example 35 and was subsequently oxidized in the same fashion as in Example 14 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.40(3H, s), 1.41(12H, s), 1.51-1.56(2H, m), 1.73-1.75(2H, m), 2.72(2H, t, J=7.8Hz), 3.64 (2H, d, J=11.7Hz), 3.85(2H, d, J=11.7Hz), 4.87(1H, br s), 5.09(2H, s), 7.05(1H, dd, J=8.3Hz, 2.9Hz), 7.19(1H, d, J=8.3Hz), 7.22-7.42(9H, m), 7.59(1H, d,J=2.9Hz)

<Example 54>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-benzyloxyphenylsulfonyl)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0113]

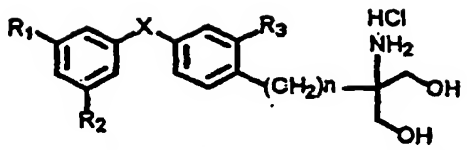


[0114] The compound of Example 53 was oxidized in the same manner as in Example 14 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.40(3H, s), 1.41(12H, s), 1.53-1.60(2H, m), 1.73-1.75(2H, m), 2.74(2H, t, J=7.3Hz), 3.64 (2H, d, J=11.7Hz), 3.84(2H, d, J=11.7Hz), 4.87(1H, br s), 5.10(2H, s), 7.15(1H, dd, J=7.8Hz, 1.5Hz), 7.31-7.53(9H, m), 7.69(1H, dd, J =7.8Hz, 2Hz), 7.86(1H, d, J=1.5Hz)

<Examples 55 through 57>

[0115] Using the compounds of Examples 52 through 54, the reactions were carried out in the same manner as in Example 36 to synthesize the compounds shown in Table 10 below.

Table 10



Example	R1	R2	R3	X	n	Yield(%)	Characteristics	FABMS $[M+H]^+$	Melting point °C
55	$PhCH_2O$	H	Cl	S	1	88	Colorless powder	430	163-165
56	$PhCH_2O$	H	Cl	SO	3	85	Pale brown amorphous	474	
57	$PhCH_2O$	H	Cl	SO_2	3	98	Brown powder	490	60-62

[0116] The following experiments were conducted to prove the effectiveness of the compounds of the present invention.

<Experiment 1>

Ability of test compounds to suppress graft host vs rejection in mice

[0117] This experiment was performed according to the method described in *Transplantation*, 55, No.3 (1993): 578-591. Spleens were collected from 9 to 11 week old male BALB/c mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). The spleens were placed in a phosphate-buffered saline (PBS(-), NISSUI PHARMACEUTICAL Co., Ltd.) or in an RPMI-1640 medium (GIBCO INDUSTRIES Inc., or IWAKI GLASS Co., Ltd.) and were either passed through a stainless steel mesh, or gently pressed between two slide glasses and then passed through a cell strainer (70μm, Falcon), to form a cell suspension. The suspension was then centrifuged and the supernatant was discarded. An ammonium chloride-Tris isotonic buffer was added to the suspension to lyse erythrocytes. The cells were then centrifuged and washed three times in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium. To this suspension, mitomycin C (KYOWA HAKKO KOGYO Co., Ltd.) was added to a final concentration of 25μg/mL and the suspension was incubated for 30 minutes at 37°C in a 5% CO_2 atmosphere. The cells were again centrifuged and washed in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium so that the medium would contain 2.5 X 10^8 cells/mL. This suspension served as a "stimulation cell suspension." Using a 27G needle along with a microsyringe (Hamilton), 20μL (5 X 10^6 cells/mouse) of the stimulation cell suspension was subcutaneously injected into the right hind footpad of 7 to 9 week old male C3H/HeN mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). A group of mice was injected with RPMI-1640 medium alone to serve as normal control. 4 days after the injection, right popliteal lymph nodes were collected and were weighed on a Mettler AT201 electronic scale (METTLER TOLEDO Co., Ltd.). Each animal was intraperitoneally administered a test compound once a day for four consecutive days starting on the day of the injection of the stimulation cells (i.e., total of 4 times). Controls were administered a vehicle that has the same composition as that used in the preparation of the test compounds. The results are shown in Table 11 below:

Table 11

Example No.	Dose (mg/kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)
36	0.03	85	45	0.3	101
37	10	92	46	0.3	80
38	10	56	47	0.3	87
39	0.3	83	48	0.3	48
41	3	89	49	0.3	63
42	10	76	51	10	50
43	10	64			

<Experiment 2>

Ability of test compounds to suppress delayed-type hypersensitivity in mice.

[0118] This experiment was performed according to the method described in *Methods in Enzymology*, 300 (1999): 345-363. 1-fluoro-2,4-dinitrobenzene (DNFB, NACALAI TESQUE Inc.) was dissolved in a mixture of acetone and olive oil (acetone: olive oil = 4:1) to a concentration of 1% (v/v). 10μL of the 1% DNFB solution was applied to the footpad of each hind leg of male BALB/c mice (JAPAN SLC Inc. or CHARLES RIVER JAPAN Inc.) for sensitization. The sensitization was done for 2 consecutive days (day 0 and day 1). On day 5, the mice were challenged with the antigen to induce delayed-type hypersensitive responses: First, the initial thickness of each ear was measured by the dial thickness gauge G (0.01-10mm, OZAKI MFG Co., Ltd.) and a test compound was administered. 30 minutes after the administration, 10μL of a 0.2% (v/v) DNFB solution was applied to the inner and outer surfaces of the right ear of each animal for antigen challenge. The left ear of each animal was challenged with the solvent alone. 24 hours after the challenge, the increase in the ear thickness was measured for each ear and the difference in thickness between the right and the left ears was determined for each individual. The test compound was dissolved, or suspended, in an ultra pure water and was orally administered at a dose of 0.1mL/10g of body weight. A control group was administered ultra pure water alone. The results are shown in Table 12 below:

Table 12

Example No.	Dose (mg/kg)	Inhibition (%)
36	1	86
37	30	87
39	3	55
49	30	81

<Experiment 3>

Activities of test compounds on skin transplantation model in mice

[0119] Effects of the test compounds were examined on skin transplantation model in mice. The experimental procedure was referred to the method described in *Journal of Experimental Biology*, 28, No.3 (1951); 385-405.

[0120] First, dorsal skin from male DBA/2 mice were stripped of the fatty layer and the panniculus carnosus and, cut into circular grafts with a diameter of 8mm. Next, graft bed, a circular area, approximately 8mm in diameter, was prepared in the back of anesthetized male BALB/c mice with a scalpel while the skin was pinched by forceps. Each graft obtained from the DBA/2 mice was placed on the graft bed formed in the backs of the BALB/c mice and was secured with a strip of adhesive bandage while held down from the top. 6 days after transplantation, the bandage was removed and the graft was subsequently observed everyday. The activity of each compound was evaluated based on the length of the graft survival period, which is defined as the number of days for rejection. Each test compound was dissolved in ultra pure water and was orally administered once a day, starting from the day of transplantation. In a similar fashion, the control group was administered ultra pure water alone.

[0121] The results are shown in Figs. 1 through 3.

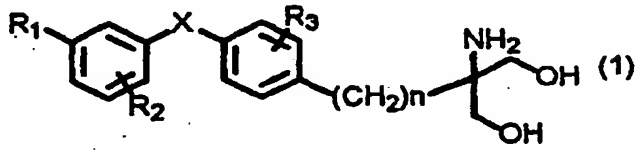
[0122] As can be seen from the results, the compounds of the present invention represented by the general formula (1) have proven effective in animal model.

INDUSTRIAL APPLICABILITY

[0123] As set forth, the present invention has been devised in recognition of the fact that the novel diaryl sulfide derivatives, in particular those in which one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other of the aryl groups includes a substituent at its meta-position, exhibit strong immunosuppressive effects. Effective immunosuppressors, the compounds of the present invention have a strong potential as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation, autoimmune diseases, rheumatoid arthritis, psoriasis, atopic dermatitis, bronchial asthma, pollinosis and various other diseases.

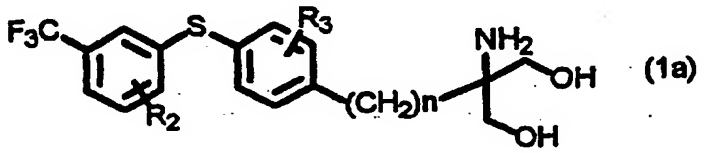
Claims

1. A diaryl sulfide derivative, a pharmaceutically acceptable salt or hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1):



wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, substituted or unsubstituted phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, or lower alkoxymethyl having 1 to 4 carbon atoms; X is S, SO, or SO_2; and n is an integer from 1 to 4).

2. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):

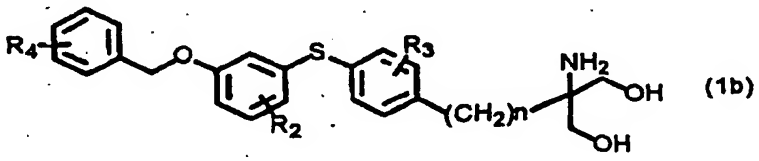


wherein R_2, R_3, and n are the same as defined above.

3. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is chlorine.

4. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is trifluoromethyl.

5. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1b):



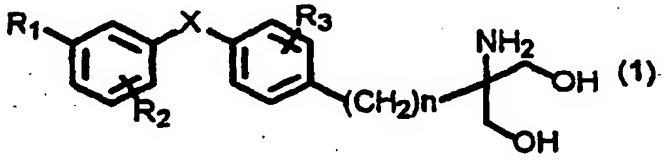
wherein R_2, R_3, and n are the same as defined above; and R_4 is hydrogen, halogen, lower alkyl having 1 to 7 carbon atoms, lower alkoxy having 1 to 4 carbon atoms, or trifluoromethyl.

6. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 5, wherein R_3 is chlorine.

7. The diaryl sulfide derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 5, wherein R_3 is trifluoromethyl.

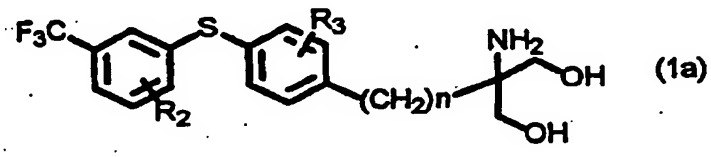
8. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is 1) 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propanediol;2)2-amino-2-[4-(3-benzyloxyphenylthio)phenyl]propyl-1,3-propanediol;3)2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol; 4) 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]butyl-1,3-propanediol; 5) 2-amino-2-[4-(3-(3'-chlorobenzyloxy)phenylthio)-2-chlorophenyl]propyl-1,3-propanediol; 6) 2-amino-2-[4-(3-benzyloxyphenylthio)-2-trifluoromethylphenyl]propyl-1,3-propanediol; 7) 2-amino-2-[4-(3,5-bistrifluoromethyl-2-chlorophenylthio)phenyl]propyl-1,3-propanediol; 8) 2-amino-2-[4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol; 9) 2-amino-2-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol; or 10) 2-amino-2-[2-trifluoromethyl-4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol.

9. An immunosuppressive agent containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and a hydrate thereof, the diaryl sulfide derivative represented by the following general formula (1):



wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, or lower alkoxymethyl having 1 to 4 carbon atoms; and X is S, SO, or SO_2; and n is an integer from 1 to 4.

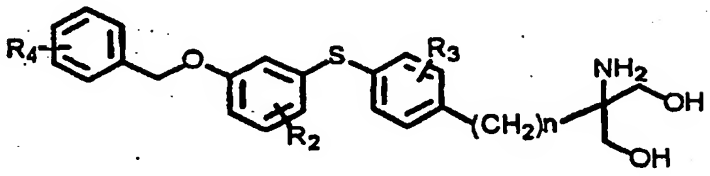
10. The immunosuppressive agent according to claim 9, containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and a hydrate thereof, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):



wherein R_2, R_3, and n are the same as defined above.

11. The immunosuppressive agent according to claim 9, containing as an active ingredient at least one of a diaryl sulfide derivative, a pharmaceutically acceptable salt and a hydrate thereof, wherein the compound of the general

formula (1) is a compound represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and n are the same as defined above; and R_4 is hydrogen, halogen, lower alkyl having 1 to 7 carbon atoms, lower alkoxy having 1 to 4 carbon atoms, or trifluoromethyl.

12. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against autoimmune diseases.

13. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against rheumatoid arthritis.

14. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against psoriasis or atopic dermatitis.

15. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against bronchial asthma or pollinosis.

16. The immunosuppressive agent according to any one of claims 9 to 11, serving as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation.

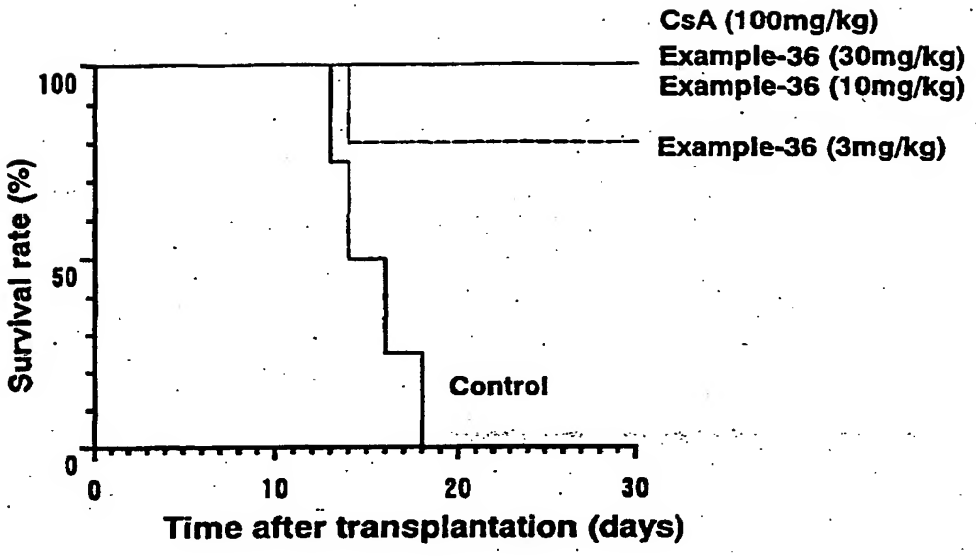

CsA (100mg/kg)
Example-36 (30mg/kg)
Example-36 (10mg/kg)
Example-36 (3mg/kg)
Control
Survival rate (%)
100
50
0
0
10
20
30
Time after transplantation (days)

FIG.1

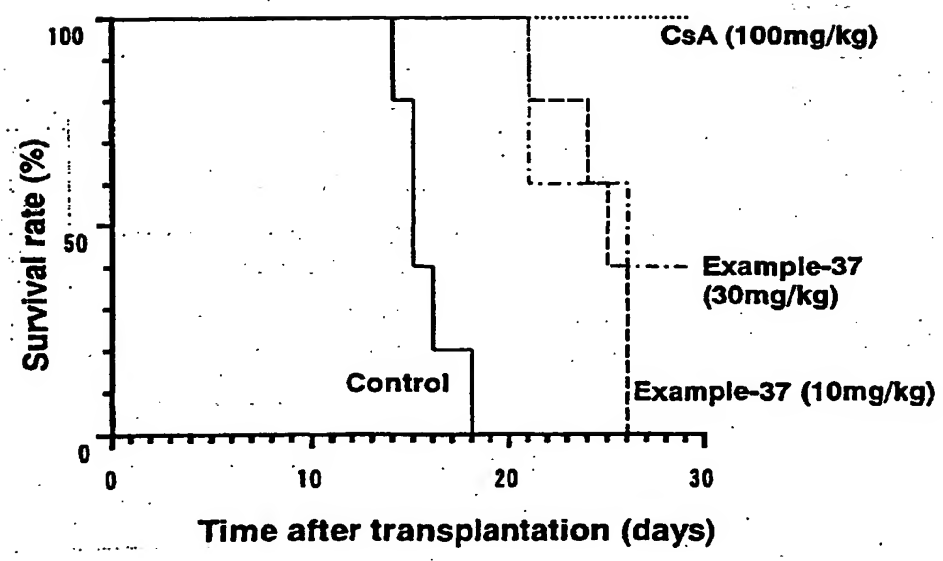

CsA (100mg/kg)
Example-37
(30mg/kg)
Example-37 (10mg/kg)
Control
Survival rate (%)
100
50
0
0
10
20
30
Time after transplantation (days)

FIG.2

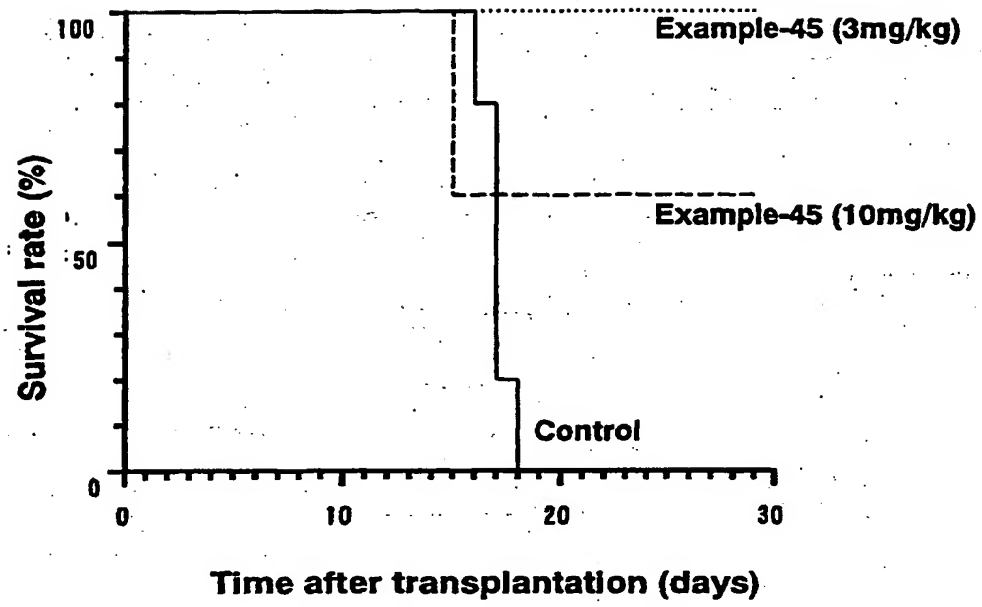

100
50
0
Survival rate (%)
Example-45 (3mg/kg)
Example-45 (10mg/kg)
Control
0
10
20
30
Time after transplantation (days)

FIG.3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09865

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C317/32, 323/32, A61K31/145, A61P11/06, 17/00, 17/06, 29/00, 37/06, 37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C317/32, 323/32, A61K31/145, A61P11/06, 17/00, 17/06, 29/00, 37/06, 37/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), REGISTRY(STN), CAOLD(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5604229 A (Yoshitomi Pharmaceutical Industries, Ltd.), 18 February, 1997 (18.02.97), Column 1, line 65 to column 3, line 50; column 67 & WO 94/08943 A1 & EP 627406 A1 & US 5719176 A & US 5952316 A & KR 155015 B1	1-16
A	EP 1002792 A1 (Yoshitomi Pharmaceutical Industries, Ltd.), 24 May, 2000 (24.05.00), Claims & WO 98/45249 A1 & AU 9865230 A & BR 9808481 A & NZ 500713 A & CN 1259117 A & US 6214873 B1 & MX 9909124 A1 & KR 2001006004 A	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 December, 2002 (06.12.02)	24 December, 2002 (24.12.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)